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Binocular coordination of saccades in Duane Retraction Syndrome

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ABSTRACT

Disconjugate oculomotor adaptation is driven by the need to maintain binocular vision. Since binocular vision in Duane Retraction Syndrome (DRS) patients is normal in half of their horizontal field of gaze (i.e., sound-side of gaze), we wondered whether oculomotor adaptive capabilities are efficient despite such a severe impairment of eye motility towards the other half of the horizontal field of gaze (i.e., affected-side gaze). We compared properties of horizontal saccades of patients with congenital unilateral Duane Retraction Syndrome type I in binocular viewing and monocular viewing conditions by simultaneously recording both eyes with the search coil technique. Our results show a mismatch between the pulse and the step signal of the innervation for saccades. When tested in the affected eye viewing condition (sound eye covered), the eyes showed not only similarly-directed increases of the saccadic gain (pulse signal) in the two eyes but also disjunctive post-saccadic drifts (step signal). This behavior suggests that visuomotor errors presented only to the affected eye were transferred to the sound eye, producing conjugate changes of the saccadic command. The post-saccadic command remained unchanged, however, and controlled the final position of each eye separately. This suggests that monocular adaptation is possible only for the step of innervation (i.e., controlling the final eye position) but not for the pulse of innervation (i.e., controlling the saccadic gain), even though the peculiarity of unilateral DRS type I offers a clear advantage for separate pathways of control for the two eyes.

1. Introduction

Because the human eyes are placed frontally, the binocular coordination of saccades is essential for achieving binocular vision after every change in fixation. In addition, binocular vision is necessary to ensure binocular oculomotor coordination via adaptive mechanisms. In humans with normal alignment and binocular vision, saccadic eye movements of the two eyes are tightly coupled and have virtually identical dynamic behavior under binocular and monocular viewing conditions (Collewijn, Erkelens, & Steinman, 1988). Interestingly, little is known about the dynamic behavior of binocular coordination of saccades in patients with strabismus, but recent studies have described impairment of the binocular coordination of saccades in strabismic patients (Bucci, Kapoula, Eggert, & Garraud, 1997; Bucci, Kapoula, Yang, Roussat, & Bremond-Gignac, 2002; Kapoula, Bucci, Eggert, & Garraud, 1997). The impairment of oculomotor coordination appears to be more severe in subjects with large convergent strabismus. In contrast, there may be residual adaptive mechanisms based on peripheral binocular vision for small angle strabismus. These studies raise the importance of binocular vision for maintaining binocular oculomotor coordination between the two eyes. Unilateral Duane Retraction Syndrome (DRS) type I is a particular form of congenital strabismus characterized by severe abduction deficit secondary to hypoplasia of the VIth nucleus motoneurons. Interestingly, there is evidence based on autopsy cases that most of VIth nucleus motoneurons are absent in DRS whereas interneurons projecting to the IIIrd nucleus are preserved (Hotchkiss, Miller, Clark, & Green, 1980; Miller, Kiel, Green, & Clark, 1982). DRS is unique in causing narrowing of the palpebral fissure on adduction with globe retraction secondary to cocontraction of both medial and lateral recti muscles on the affected side. Indeed, there is evidence that the lateral rectus muscle of the affected eye is partially innervated by branches from the inferior oculomotor nerve (IIIrd) as supported by early electromyographic studies (Alexandrakis & Saunders, 2001; DeRespinis, Caputo, Wagner, & Guo, 1993; Gurwood & Terrigno, 2000; Gutowski, 2000; Jampolsky., 1999; Metz, 1982; Raab, 1986). Contrary to concomitant strabismus, DRS presents the opportunity to study binocular coordination of saccades. Indeed, unilateral DRS is characterized by a severe incomitant eye misalignment in one half of the horizontal field of gaze (i.e.,

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affected-side gaze). The ability of fusion and normal binocular vision with stereopsis is maintained, however, in the other half of field of gaze (i.e., sound-side gaze). We have previously described and discussed the properties of saccades in unilateral DRS type I in *binocular viewing conditions* (Yuksel, Optican, & Lefevre, 2005). In this earlier study, centrifugal and centripetal saccades toward the affected-side or sound-side gaze were analyzed separately. In all conditions, it was shown that there was a strong coupling of the saccadic command for the affected and the sound eye. As both eyes were characterized by completely different innervational and mechanical properties, there was a consistent misalignment of the two eyes at the end of saccades. The adaptation of the post-saccadic command allowed fusion of both eyes on the target by means of disconjugate post-saccadic drifts. These findings allowed us to propose a model of common conjugate saccadic drive signal for the two eyes with the possibility for the post-saccadic command to adapt separately for each eye.

The goal of the present study was to further investigate the binocular control of horizontal saccades and the related adaptation mechanisms by systematically comparing saccades in *monocular viewing conditions* and in *binocular viewing conditions* in unilateral DRS patients. We will first assess whether there is a possibility to adapt saccades in monocular viewing in DRS. If found, we will investigate whether there is a transfer of the adaptation to the other (occluded) eye. Finally, depending on the type of adaptation (the pulse and/or step component of saccadic command) and the presence of transfer to the other eye, we hope to shed light on saccadic adaptation mechanisms in a theoretical framework. In conclusion, this study will contribute to a better understanding of monocular versus binocular and saccadic versus post-saccadic adaptation mechanisms of saccades.

2. Methods

2.1. Subjects

The patient inclusion criteria were based strictly on clinical features. Horizontal ocular motility was typical of *congenital unilateral DRS (type I)*. There was a severe limitation of abduction of the affected eye toward the affected side gaze. Globe retraction and palpebral fissure narrowing was present in adduction toward the sound side gaze, which characterized the anomalous innervation of the affected lateral rectus muscle. There was no abnormal head posture, and eyes were perfectly aligned in the primary position with normal binocular vision. Ocular motility of the sound eye was unremarkable. Two subjects were selected for study (LT and MB). For subject LT, the left eye was affected, and, for subject MB, the right eye was affected. Eye dominance was tested with fixation to a target at a far distance through a small center hole approximately 5 mm in diameter held with the arms in a straight ahead position. The eye used to fixate to the target was considered to be the dominant eye. Both subjects showed left eye dominance, corresponding to the sound eye for subject MB and to the affected eye for subject LT. No ocular or systemic anomalies were associated to the oculomotor disorder, and no previous strabismus surgery had been performed on these patients. The binocular vision was tested in the half of their horizontal field of gaze in which the eyes were aligned. There was normal peripheral and central fusion in the Worth test and normal values of stereoacuity in the TNO test (60 s of arc). Snellen visual acuity was 6/6 at far and near for each eye with proper myopic correction for subject MB. There was no anisometropia and no amblyopia. Anterior and posterior segment examination of the eyes showed no abnormalities.

2.2. Data acquisition and analysis

Subjects were seated in complete darkness with their head restrained by a chin-rest. They faced a 1-m distant tangent screen, which spanned approximately 45 deg of the visual field. The visual target was a red laser spot back-projected onto the screen and moved horizontally under the control of a mirror-galvanometer. Horizontal saccades from both eyes were recorded simultaneously with the scleral search coil technique (Skalar Medical BV). All subjects gave informed consent, and all procedures were approved by the Université catholique de Louvain Ethics Committee.

Eye and target position were sampled at 500 Hz and stored on the hard disc of a PC for off-line analysis with MATLAB (Mathworks, Inc.). Position signals were low-pass filtered by a zero-phase digital filter (autoregressive forward-backward filter, cutoff frequency: 50 Hz). Velocity and acceleration were derived from position signals using a central difference algorithm. For the study of an oculomotor disorder such as DRS, it seems inadequate to apply the same detection criteria to the two eyes because the kinematics of the affected eye are drastically different from those of the sound eye. The distinction between the fast and the slow part of the eye movement becomes ambiguous for the mechanically affected eye. Therefore, the detection of the saccade of the affected eye was based on the onset and offset of the saccade of the sound eye. In our analysis, saccade onset was detected based on an acceleration threshold of 750 deg/s^2 on the sound eye. Saccade offset was detected if eye acceleration fell below the same acceleration threshold for at least 30 ms (to make a clear distinction between multiple saccades and abnormal saccades).

2.3. Oculomotor testing paradigm

A standard saccade paradigm was used to elicit horizontal saccades. Subjects were instructed to fixate as accurately as possible on target while their heads were restrained in the chin rest. The goal was to generate centrifugal and centripetal saccades in the right and left directions. For this purpose, subjects fixated on a small central spot of red light during a randomized period of 300–800 ms. The target then appeared in the periphery at a randomly chosen position extending from 0 to 20 deg either to the left or right from the center. After a randomized duration of fixation between 600 and 1600 ms, the target returned back to the central position of fixation.

The position of both eyes was recorded simultaneously in *binocular and monocular viewing conditions* (right eye viewing or left eye viewing). Trials for each type of viewing condition were performed on different days with one week intervals between each session. For binocular viewing conditions, subjects were asked to fixate on the target with both eyes open without inferring which eye should fixate preferentially. For monocular viewing conditions, the occlusion of either the sound or the affected eye started 30 to 60 min before the experiments. Recordings in the affected eye viewing condition were performed with the sound eye occluded, and vice-versa. Subjects were asked to read actively during the occlusion period before the experiments started. The eye remained occluded during the whole experiment except during the short delay of coil placement on the eye. During this procedure, careful attention was given to keep the other eye occluded to avoid any binocular viewing before and during the recording.

2.4. Qualitative and quantitative analysis

Only centripetal affected-side gaze saccades were considered for detailed comparative analysis between data obtained in binocular and monocular viewing conditions (Fig. 1). Indeed, it is appropriate to study horizontal saccades directed to the *affected-side*

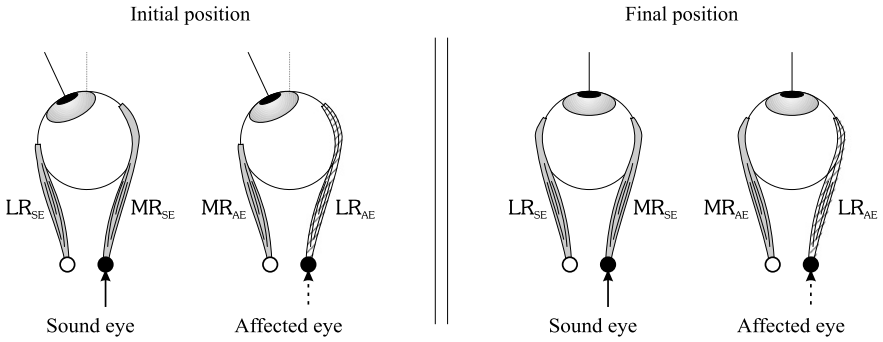

Fig. 1. The schematics illustrate the left and right eye during movements from an eccentric position located in the sound side (initial position) toward the central fixation position (final position). It represents movement of the eyes toward the affected-side gaze in centripetal direction with good alignment between the two eyes. The horizontal recti muscles of each eye are drawn with abnormal innervational input for the LR of the affected eye. LR_{SE} = Lateral Rectus muscle of the sound eye, MR_{SE} = Medial Rectus muscle of the sound eye, LR_{AE} = Lateral Rectus muscle of the affected eye, and MR_{AE} = Medial Rectus muscle of the affected eye.

gaze (ASG) because it implies innervation from the deficient VIth nerve motoneurons. The motor command drives the affected eye toward abduction via the neural activity from the deficient VIth nerve motoneurons and the sound eye toward adduction via the neural activity from the intact VIth nerve interneurons (Yuksel et al., 2005). *Centrifugal* ASG eye movements of the affected eye are characterized by severe limitation of motility with very low saccadic gain and, thus, were not appropriate for a quantitative analysis (see Fig. 4A in Yüksel et al., 2005). *Centripetal* ASG eye movements were considered to be more appropriate for studying saccadic properties in the deficient side of gaze. Indeed, the range of amplitude of centripetal saccades to affected-side gaze is wider because the relaxation of the antagonist medial rectus muscle contributes significantly to saccades in this condition. Despite the innervational deficit, the range of saccadic amplitudes is still large enough for studying the properties quantitatively. In our study, saccadic gain was calculated from the ratio of the primary saccade amplitude to the target displacement. Unitary gain was representative of an accurate saccade that perfectly reached the target.

The *affected side* gaze concerns the eye movements toward the *left* for subject LT and toward the *right* for subject MB. For descriptive purposes and to make comparison between the two subjects easier, the traces of the recordings concerning subject LT have been inverted. Therefore, eye movements directed from negative to positive values of the eye position represent eye movements toward the affected-side gaze for both subjects. Saccades were categorized into *centripetal or centrifugal* according to whether they were directed towards or away from the primary position. Centripetal movements towards the affected-side gaze concerned adducting saccades of the sound eye and abducting saccades of the affected eye. Each category of eye movements showed a fast saccadic phase, detected by the acceleration criterion, and is represented in bold on the figures. It was followed by a post-saccadic smooth eye displacement *(post-saccadic drift)* on the affected eye or the sound eye, either in an *onward* or *backward* direction relative to the saccade (Fig. 2).

Saccades were categorized as *normal* if there was a single peak in eye velocity and categorized as *abnormal* in all other cases. Only normal saccades were included in the quantitative analysis (85%). The occurrence of anticipatory saccades was minimized by randomization in time, direction, and position step of the target. All saccades with latency shorter than 120 ms were excluded from the analysis (10% of trials).

3. Results

Typical binocular centripetal saccades directed towards the affected-side gaze are shown for subjects MB and LT in Fig. 2. Trials were subdivided into three viewing conditions: BV (binocular viewing), SEV (sound eye viewing) and AEV (affected eye viewing). In the *BV condition* (Fig. 2A), both eyes reached the target despite the reduced innervation toward the affected-side gaze. The sound eye, which is driven by the innervation through the VIth nerve interneurons, showed an accurate saccade with no post-saccadic drift. Saccade amplitude of the affected eye was inaccurate and undershot the target. The fast saccadic component was followed by a systematic post-saccadic onward drift of the affected eye, correcting the disconjugacy between both eyes. In the *SEV condition* (Fig. 2B), the characteristics of the saccades of both eyes were similar compared to BV conditions, besides a small misalignment between both eyes resulting from the lack of binocularity in the monocular viewing condition. The similarity between saccadic behavior in BV and SEV conditions indicates that there is little adaptation in SEV. In short, the BV condition is optimized for the sound eye. In the *AEV condition*, we observed two features of oculomotor behavior: either recordings showed one single overshooting saccade on the sound eye with undershoot of the affected eye (Fig. 2C) followed by disconjugate post-saccadic drifts in opposite directions for the two eyes, or they showed staircase behavior with multiple normal saccades on both eyes (Fig. 2D). In AEV, the affected eye reached the target through an undershooting saccade followed by an onward post-saccadic drift whereas the sound eye overshot the target and smoothly drifted back. The general behavior was similar for the two subjects, with the exception of an offset between both eyes for subject LT.

3.1. The fast component of the saccade in the monocular viewing condition

The sensory visual input for programming a saccade is the position error (Δ) of the viewing eye (=ΔSE for the sound eye or ΔAE for the affected eye) with respect to the target. In the AEV condition, sensory visual error information is given by the affected eye. Since there is a congenital hypoplasia of sixth nerve motoneurons driving the eye toward the affected-side gaze, we did not expect that the oculomotor system could respond to this consistent visual error by adaptive mechanisms, which would lead to a change in innervation for the affected eye. Quantitative analysis of the data demonstrates, however, an increase in saccadic gain for the affected eye in the AEV condition. Fig. 3 illustrates the relationship of the mean of saccade amplitude of the affected eye and the sound eye in AEV versus BV conditions. Means of saccadic amplitude for each eye were calculated in two degree bins of target step amplitude. The reference value for a gain equal to one is represented by the solid line corresponding to no change in saccadic gain between BV and AEV conditions. Plots of bi-directional 95% confidence intervals show a clear increase in the saccadic amplitude for the affected eye in the AEV condition. This is shown by

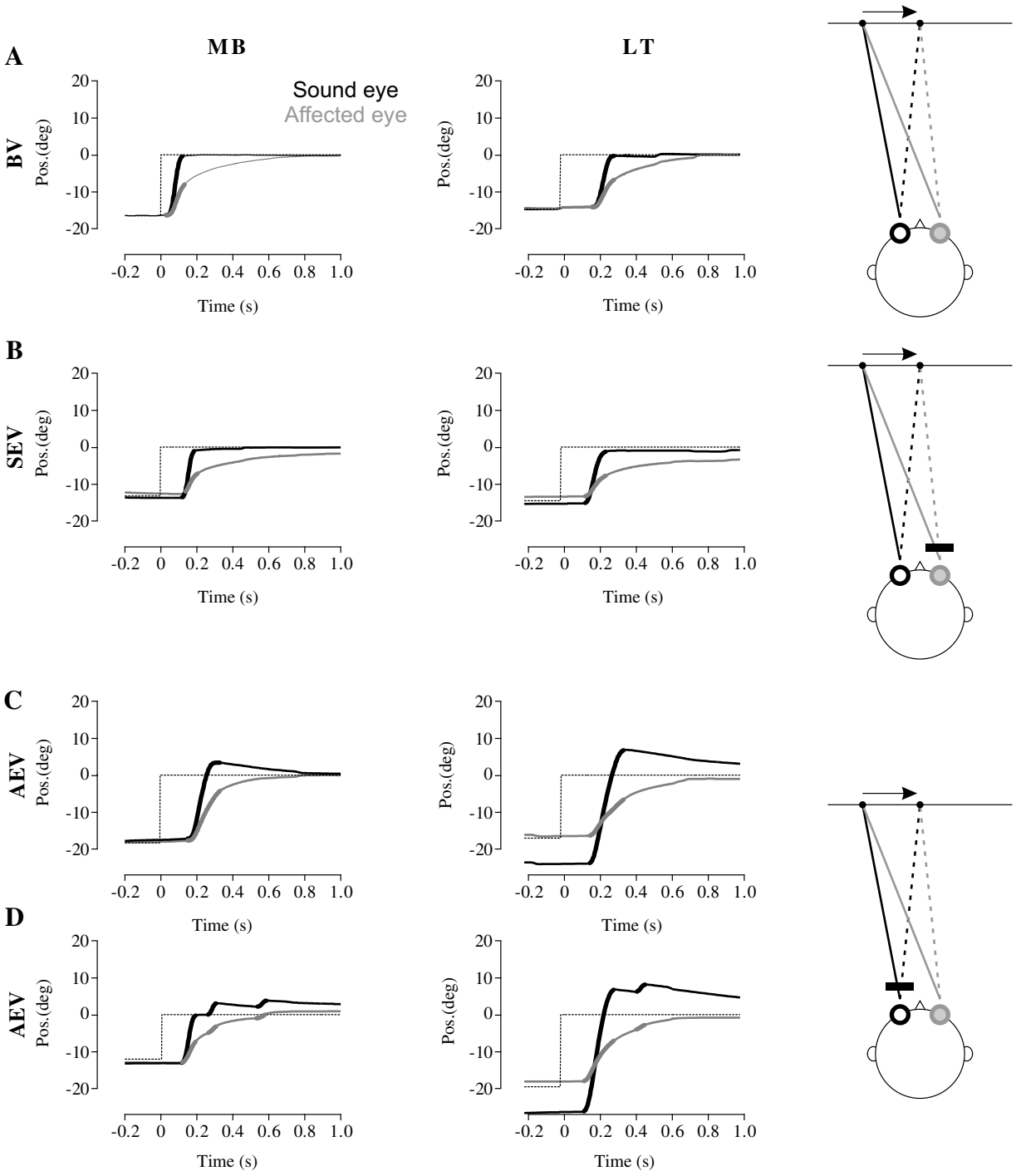

Fig. 2. Typical traces of centripetal eye movements toward the affected-side gaze, recorded with the search coil technique, for each subject and in different viewing conditions (BV, SEV, AEV). Positive horizontal eye position corresponds to the affected-side gaze. Negative horizontal eye position corresponds to the sound-side gaze. (A) A typical binocular viewing (BV) recording for subject MB and LT. (B) A typical sound eye viewing (SEV) recording for subject MB and LT. (C) A typical affected eye viewing (AEV) recording for subject MB and LT with behavior of saccadic gain >1. (D) A typical AEV recording for subject MB and LT with a staircase behavior. The diagrams on the right part of the figure illustrate the target movement in centripetal direction from sound-side gaze (left on the diagram) toward the affected-side gaze (right on the diagram). Subject fixates the target in an eccentric position (left dot). Target is extinguished and appears in the center fixation position (right dot). The task induces centripetal abducting saccades for the affected eye and centripetal adducting saccades for the sound eye. Search coils measure eye position of the two eyes simultaneously. Viewing conditions include; BV = binocular viewing (both eyes open), AEV = affected eye viewing (sound eye occluded) and SEV = sound eye viewing (affected eye occluded). Subjects used the viewing eye to track the target while eye movements were measured simultaneously in the viewing and the non-viewing eye. The eye patch is represented by a black rectangle lying before the occluded eye.

the distribution of all the blue data points above the reference line for unitary gain between both viewing conditions. Interestingly, the increase in saccadic gain affects the sound eye similarly to the affected eye. The increase in the gain of the sound eye can be quantified for bins of larger amplitude (see Fig. 2). Since this analysis shows a similar increase in the saccadic gain for the sound eye and the affected eye, it indicates that the pulse signal is increased for the two eyes. The increase in innervation of the sound eye by

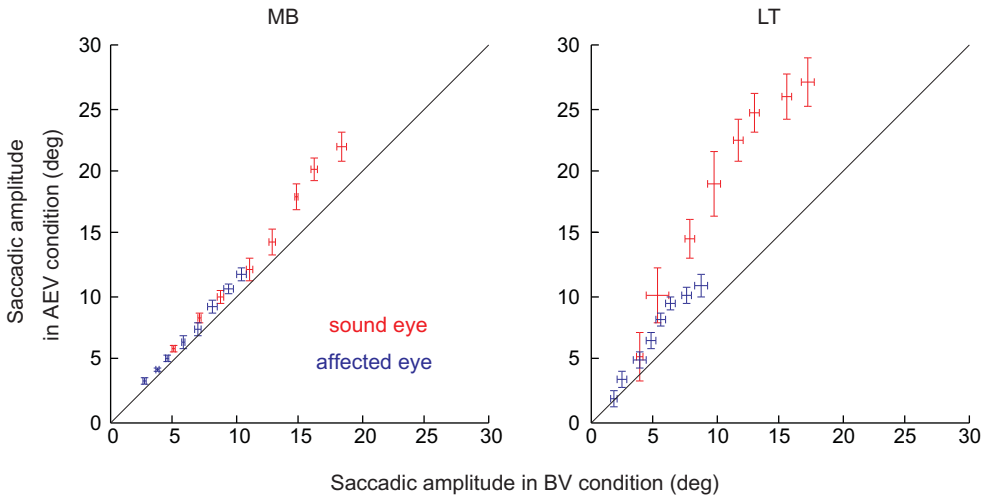

Fig. 3. The diagram represents the relationship between the saccadic amplitude in the AEV condition and the saccadic amplitude in the BV condition for each subject and for each eye. Means of saccadic amplitudes for each eye in AEV vs. BV conditions and for each subject were calculated for two degree bins of target step amplitude. For each bin of step amplitude, bi-directional 95% confidence intervals were drawn for each eye (affected eye in blue and sound eye in red) in BV and AEV conditions.

transfer of adaptation from the affected eye is illustrated in Fig. 4. The graph shows a linear relationship between the position error provided by the affected eye (ΔAE) and the saccade amplitude of the sound eye in both BV and AEV recordings. The slope of the linear regression is indicative of the saccadic gain of the sound eye. In the BV condition, traces of recordings (see Fig. 2A) show an accurate saccade of the sound eye, implying an appropriate calibration of the innervational signal. Indeed, the slope of the regression, which is indicative of saccadic gain, is 0.93 (MB) and 1.07 (LT) in the BV condition. The comparison of data acquired in affected eye viewing (AEV) and binocular viewing (BV) conditions shows a clear increase in saccadic amplitude for the sound eye, which implies an increase in innervation (see Fig. 2C–D). Indeed, the slope of the linear regression in Fig. 4 increases from 0.93 to 1.19 for subject MB and from 1.07 to 1.77 for subject LT. Results indicate that there is a transfer of the innervation sent from the affected eye towards the sound eye. This is illustrated by an increase in saccadic gain of the sound eye in the AEV condition compared to the BV condition. In conclusion, the adaptation of the pulse signal is "yoked" for the two eyes without separate adaptation.

3.2. The slow post-saccadic drift in the monocular viewing condition

The saccadic and post-saccadic motor commands must be correctly matched to produce an accurate saccade and steady fixation following it. The post-saccadic innervation, often referred to as the step signal, is necessary for overcoming the elastic restoring forces of the eye muscles and is responsible for maintaining the steadiness of the eye in between saccades. The saccadic motor command, often referred to as the pulse signal, is responsible for overcoming the viscous forces during saccades. Saccades in DRS illustrate a mismatch between the pulse and the step of innervation. There is indeed a systematic post-saccadic drift of the affected eye in all viewing conditions. A mismatch appears for the sound eye when there is an increase in the pulse signal of innervation in the AEV condition. Importantly, in all viewing conditions, even when the pulse signal has been increased, the step signal of innervation for each eye remains unaffected and well adapted to the target step. Consequently, when the saccade does not reach the target, it is followed by a post-saccadic drift driving the eye to the target, i.e., the final eye position (see Fig. 2). This is illustrated in Fig. 5. Means of eye velocity and position error at the end of the saccade were calculated and plotted with bi-directional 95% confidence intervals for the two subjects (Fig. 5) for the affected eye and for the sound eye in the AEV condition. For the affected eye, undershooting saccades are followed by an onward drift (positive eye velocity in Fig. 5). In contrast, for the sound eye, overshooting saccades are followed by a backward drift (negative eye velocity in Fig. 5). Data in the AEV condition are in favor of the hypothesis that there is saccadic adaptation in the AEV condition with an increase

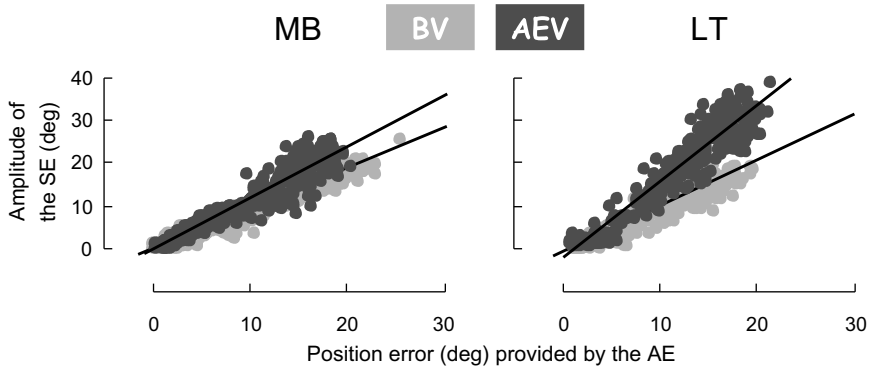

Fig. 4. Linear relationship is represented for each subject for centripetal saccades to affected-side gaze between the position error coming from the affected eye and the saccade amplitude of the sound eye. Plots are drawn in black for the affected eye viewing condition (AEV) and in grey for the binocular viewing condition (BV). The equations of the linear relationship are: $y = 0.39 + 0.93x$ ($N = 862$, $r = 0.98$, $p < 0.01$) for subject MB, $y = -0.54 + 1.07x$ ($N = 309$, $r = 0.92$, $p < 0.01$) for subject LT in *BV condition*, and $y = -0.04 + 1.19x$ (N=419, $r = 0.95$, $p < 0.01$) for subject MB, $y = -2.48 + 1.77x$ ($N = 311$, $r = 0.95$, $p < 0.01$) for subject LT in the *AEV condition*.

in the pulse signal sent to the two eyes without affecting the step signal, which remained unchanged and adapted separately for each eye.

4. Discussion

4.1. Conjugate adaptation of the pulse and disconjugate adaptation of the step

We previously discussed the controversy concerning the source of the neural command to make a conjugate saccade and proposed a model of the pulse-step innervation command with the possibility to adapt the step separately for the two eyes (gain K, see Fig. 6) (Yuksel et al., 2005). Since our experimental paradigm required only monocular viewing in the AEV condition, there were no visual cues causing ocular misalignment and, therefore, no vergence input. Results showed that adaptive mechanisms may be engaged to enhance the innervations of the affected eye in the AEV condition (Fig. 3). Moreover, the increased signal of innervation was transferred to the sound eye (Fig. 3). Analysis of performance of the sound eye with a systematic comparison with the affected eye demonstrates adaptive changes in central oculomotor innervation, leading us to better localize the level of adaptation. Saccadic adaptation could, in fact, occur at three different levels in the simplified model of pulse-step of innervation (Fig. 6). First, the increase in innervation in the AEV condition may occur at a high level upstream from the brainstem neural controller (Fig. 6A, gain K_{AEV}). This would correspond to a classical type of saccadic adaptation, without any pulse step mismatch. Our results clearly do not support this hypothesis. It would imply the same amount of adaptation for the pulse and the step with an increase in innervation of the two signals. Thus, there would be no backward post-saccadic drift in the sound eye if the step signal was increased proportional to the increase in the pulse signal. On the contrary, our results show that the innervation of the step remains unchanged for each eye (see Fig 2). The second possible site of adaptation is more peripheral, with the possibility to adapt the pulse only for the affected eye, implying an independent control for the two eyes (Fig. 6B, gain K_{AEV}). Unilateral DRS would be an excellent candidate for this type of adaptation as it is a congenital unilateral peripheral deficit of motoneurons that would give a clear advantage for independent control. Our results, however, clearly show an increase in saccadic amplitude for the two eyes in the AEV condition, implying an increase of the pulse of the innervation signal in the same proportion for the two eyes. The last hypothesis implies a yoked adaptation for the pulse signal of the two eyes (Fig. 6C, gain K_{AEV}) with an unchanged gain in the step signal, which remains adapted separately for each eye (Fig. 6C, gain K). Recordings in all viewing conditions contribute to the conclusion that there is no way to adapt the pulse signal separately for the two eyes. Moreover, an independent control of the step signal for the affected eye exists and remains unchanged in all viewing conditions. Our hypothesis is illustrated in Fig. 6C.

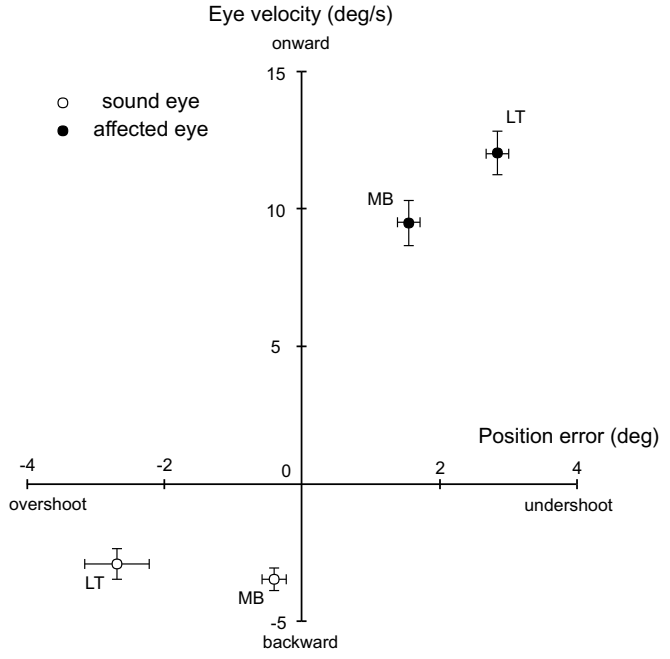

Fig. 5. Means of eye velocity (deg/s) versus means of residual position error (deg) at the end of the saccade were plotted with bi-directional 95% confidence intervals for each subject (MB, LT), for the affected eye (filled symbols) and the sound eye (open symbols). Positive eye velocity values correspond to an onward post-saccadic drift and negative eye velocity values to a backward post-saccadic drift. Positive values of position error represent an undershooting saccade and negative values of position error an overshooting saccade.

The pulse and step of innervation must be correctly matched to produce an accurate eye movement and steady fixation following it. If the pulse and step are not matched correctly, the eyes will drift from the position reached after the pulse to that which corresponds to the step (Leigh & Zee, 2006; Robinson, 1963; Robinson, 1973). Compensation from the saccadic system for poor eye movement performance has been previously described in both man and monkey (Abel, Schmidt, Dell'Osso & Daroff, 1978; Albano & King, 1989; Kapoula, Optican, & Robinson, 1989; Kapoula et al., 1997; Kommerell, Olivier, & Theopold, 1976; Optican & Robinson, 1980; Optican, Zee, & Chu, 1985; Snow, Hore, & Vilis, 1985; Viirre, Cadera, & Vilis, 1988; Wong, McReelis, & Sharpe, 2006). There is some evidence for multiple concurrent adaptive processes, operating at both monocular and binocular levels. Recently, (King & Zhou, 2000; Zhou & King, 1998) demonstrated evidence for binocular and monocular neural commands at the motor and premotor levels. These results are of particular interest because they are compatible with monocular control and adaptation of saccades. Many characteristics of the congenital deficit in DRS (the different mechanical properties of the two eye plants and the normal sensorial status) would give independent motor commands a significant advantage in controlling eye movements. However, our results do not plead in favor of the monocular control of the saccadic pulse.

Differences in repair properties of the sixth nerve in chronic *peripheral* versus *central* palsies have been investigated, and there is evidence for monocular unidirectional change in saccade speed in the paretic eye after peripheral palsy but not after central palsy (Wong et al., 2006). Monocular changes in peak velocity were either due to regeneration of axons/myelin peripherally or due to mechanisms of monocular adaptation. These mechanisms of adaptation seem to be damaged in central palsies. Regarding these results, it seems reasonable that we found no evidence for monocular adjustments of the innervation signals. Indeed, DRS is a congenital maldevelopment of sixth nerve motoneurons with no possibility for regeneration of axons or myelin. Moreover, the deficit concerns central motoneurons with the possibility of damage to monocular adjustment mechanisms.

The amount of yoking between the two eyes when only one eye receives visuomotor errors was studied using the technique of intra-saccadic target displacements in normal human subjects (Albano & Marrero, 1995). Rapid adaptive changes trained monocularly were shown to be transferred to the non-viewing eye. Authors have suggested that recalibration of the saccade occurs quickly as a conjugate adjustment of gain, which is used to balance innervations to the two eyes. Thereafter, disconjugate mechanisms have been implicated for providing a further recalibration to each eye

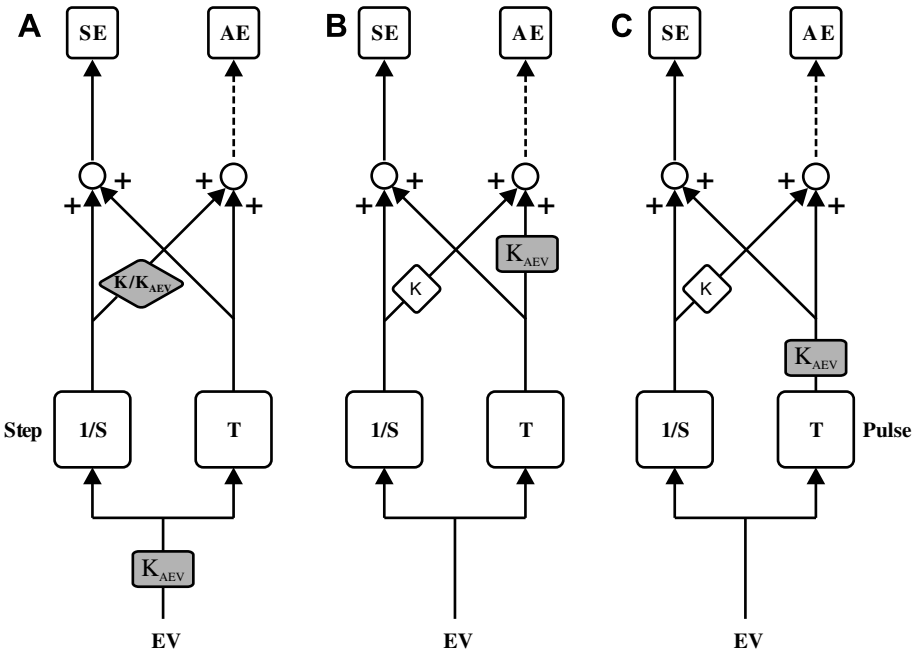

Fig. 6. The innervation results from an association between the pulse and the step signal. The distribution of the innervations signal to the two eyes is represented by this diagram. Each signal of pulse and step is directed towards each eye. The motor input from the abducens motoneurons toward the affected eye is drawn as a dotted line. The step to the affected eye is adapted through gain K as described earlier. Three different hypotheses for the level of adaptation through gain K_{AEV} (drawn in grey) are illustrated in the diagrams. (A) Represents an adaptation (gain = K_{AEV}) upstream from the brainstem neural controller, which is the same for the pulse and the step for the two eyes. (B) A separate adaptation for the pulse (gain = K_{AEV}) and the step (gain = K) independently for the two eyes. (C) Illustrates a possibility of adaptation for the pulse (gain = K_{AEV}) signal coupled for the two eyes and the ability to adapt the step signal separately.

independently. We described a similar transfer of adaptation (increase of saccadic gain) from the affected eye (receiving the visuomotor error) to the sound eye (which is covered) after prolonged monocular viewing with the affected eye in unilateral DRS patients. We systematically compared saccades of the two eyes. This study yields more evidence that saccadic gain is adjusted on the viewing eye (either affected eye or sound eye) in monocular viewing trials and that there is a conjugate yoked transfer of the adaptive mechanism for the saccadic gain. Yet, unilateral DRS type I offers an advantage for independent monocular control with the ability, to some extent, to enhance affected eye saccadic gain (Fig. 3). On the contrary, the step signal of innervation can be adapted separately from the pulse signal and is independent for each eye. The final intended eye position is therefore maintained with both eyes on the target, achieving normal binocular vision.

4.2. Are there separate neural pathways for adaptation of the pulse and step of innervations?

The neurophysiological substrate for the site of adaptation for saccades is still debated. It has been suggested from studies using experimental lesions in monkeys (Barash, Melikyan, Sivakov, Zhang, Glickstein & Thier, 1999, Goldberg, Musil, Fitzgibbon, Smith, & Olson, 1993, Optican & Robinson, 1980; Takagi, Zee, & Tamargo, 1998) and cerebral functional imaging in humans (Desmurget, Pelisson, Grethe, Alexander, Urquizar, Prablanc & Grafton, 2000; Desmurget, Pelisson, Urquizar, Prablanc, Alexander & Grafton, 1998) that the cerebellum plays a major role in saccadic adaptation. Previous research has reported that the burst discharge of neurons in the SC does not change during saccade adaptation, encoding the desired saccade size and not the size of the adapted saccade (Edelman & Goldberg, 2002; Frens & Van Opstal, 1997). The site of adaptation has been suggested to occur upstream from the caudal fastigial nucleus (CFN), the output of the oculomotor cerebellar vermis, (Scudder & McGee, 2003) but downstream to the superior colliculus (SC). Recently, changes in activity in the nucleus reticularis tegmenti pontis (NRTP) have been reported during saccadic adaptation (Takeichi, Kaneko, & Fuchs, 2005). This structure is a major source of afferents to both the oculomotor vermis and the CFN and receives, in turn, direct input from the SC. The principal deficit in monkeys after cerebellar lesions is the inaccuracy of the pulse and step of innervation to the target displacement. Therefore, the major role of the cerebellum in saccadic eye movements seems to be the adjustment of the gains of the pulse- and step-generating mechanisms. Studies performed with partial cerebellectomies in monkeys described the importance of the vermis, the paravermis and the fastigial nuclei in adaptive control of the *pulse* signal of innervation. The midline cerebellum appears to be important for repair of saccadic dysmetria but not for repair of post-saccadic drift (Goldberg et al., 1993; Optican & Robinson, 1980; Takagi et al., 1998). In contrast, studies performed with bilaterally flocculectomized monkeys suggest that the adaptive control of the *step* of innervation depends on the flocculus and paraflocculus (Optican & Robinson, 1980; Optican, Zee, & Miles, 1986). It is reasonable to assume that this neurophysiological pathway could play a central role in the adaptation reported in the present study. Thus, we hypothesize that the vermis, which is a midline structure shared by the two sides of the cerebellum, could be involved in an increase in the *pulse* signal of innervation (gain = K_{AEV} in Fig. 6C) yoked for the two eyes. Moreover, the possibility of independent control of the *step* signal for the affected eye (gain = K in Fig. 6C) suggests the existence of a bilateral neurophysiological substrate with independent pathways for the two eyes. Cerebellar flocculi and paraflocculi could be very good candidates for this process.

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